sites and known functions of the Hedgehog/Patched pathway in development. Finally, loss of the normal ptc allele during adult life leads to multiple foci of basal-cell carcinoma.

It will be important to test whether homologous loss of the ptc gene also occurs in the sporadic form of basal-cell carcinoma (BCC), which is the most common type of human cancer (750,000 estimated cases in the United States per year). Preliminary studies show that in 3 out of the 12 BCC tumours examined so far, the ptc region has been lost from one chromosome and there are mutations in ptc on the other.

The role of Patched as a tumour suppressor reveals new roles for the Hedgehog/Patched pathway, and suggests that Hedgehog is involved in the induction of cell proliferation in several adult tissues. Three conserved Hedgehog genes (sonic, desert and indian) have been identified in higher vertebrates, all of which are capable of activating the same pathway. It would be interesting to find out which of the three is expressed in skin. The common function of Patched in various developmental contexts and in different organisms is to suppress the expression of specific genes. Are these target genes similar during development and in the adult skin? Would the generation of small clones homozygous for a defective ptc gene also lead to tumour growth in Drosophila?

So ptc represents the first developmental gene that is also a tumour suppressor. Other developmental genes such as Wnt1 and Gli (human glioblastoma gene, the homologue of the Drosophila Ci gene) were initially identified as oncogenes. In fact, both of these genes appear to be direct or indirect targets for repression by Patched, which may explain why ptc is a tumour-suppressor gene whereas they are oncogenes. In contrast to the Rb and p53 tumour-suppressor proteins which interact in the nucleus with components of the cell-cycle clock, Patched is a membrane protein regulating a complex cytoplasmic cascade terminating in transcriptional repression. Future research will tell us just how the Patched pathway impinges on the regulation of the cell cycle.

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**FIG. 1** Water in turbulent motion. A jet flowing through a circular hole into a tank of still water is made visible using a fluorescent dye, illuminated by a thin sheet of laser light. This snapshot shows the complex patterns that result from the turbulent fluid motion. (From the laboratory of K. Sreenivasan, Yale University.)

A BREEZE swirls around with velocities that vary wildly in space and time — like many other physical systems, it is turbulent. Despite its familiarity and ubiquity, turbulence is ill understood. It presents two problems at once: determining flow velocities and figuring out how completely these velocities mix constituents suspended in the flow. But after decades of ambiguous results, two papers now bid fair to tell us the range of these turbulent fluctuations, a vortical motion develops, and these swirls quickly generate new vortices. Soon there is an avalanche of complexity (Fig. 1). This turbulent motion governs blood flow through arteries, weather patterns, air flow past rapidly moving vehicles and the chaos at the surface of the Sun.

Long ago we gave up the notion that we could make accurate, detailed, long-term predictions in turbulent situations. Instead, we aim for the more modest goal of estimating the probability of the various kinds of events which might occur in a fluid. Applied work estimates the probability of interesting events — whether rain will fall tomorrow, for example. More fundamental studies concentrate on simpler events, such as the probability of observing a certain value of the difference in fluid velocity or contaminant concentration between two closely spaced points. For example, one can use an experimental picture of the mixing of two fluids (Fig. 2) to determine the probability of finding both fluids within a specified short distance.

The fundamental theory of turbulence was set forth in two papers by Kolmogorov published in 1941 and 1962 (and reviewed in ref. 2). Both of these describe the probabilities for observing the different possible values of \( \Delta u(r) \), the velocity difference between two points separated by a distance \( r \). The two Kolmogorov papers sketch out two quite different theories. The earlier one assumes a situation of 'simple scaling' in which the fluctuation in \( \Delta u \) has a 'typical' magnitude, predicted to vary as \( r^{1/4} \). Events with differences far from this typical magnitude are then very improbable. In contrast, the later paper, called K62, assumes no typical value of \( \Delta u \); rather, there is a tremendous range of event sizes. A situation in which some quantity varies so wildly that it has a range of characteristic scales is described by the word multiscaling. In the years since 1962, both points of view have had champions among experimenters, theorists and simulators.

Nianzheng Cao and colleagues make a computer simulation in a periodic box and measure the probability distribution of sizes of \( \Delta u \). They find far more variation than allowed by the K41 theory, and the number of outlier events can be fitted
quantitatively using a multiscaling theory. The practical implications of this result are that engineering design must take into account a huge range of possible values of every turbulent quantity. This wide variation can make all kinds of tasks harder, complicating the life of both the aeroplane designer and the scientist trying to simulate turbulent flow. On the other hand, the computation does provide support for some of the standard methods used to simplify numerical computations of turbulence, including large-eddy simulations.

Swirling fluids can also carry things around—other fluids or solids or heat, for example—which move and mix under the combined influence of the fluid motion and their own diffusion. Important issues, for example the extent of chemical reactions, depend on the degree of mixing of these passive constituents, and turbulence is crucial in obtaining good mixing. Recent calculations have concentrated on fluctuations in the spatial distribution of temperature differences, driven by rapid variations in the prescribed velocity field. The rapidity of the fluctuations makes the calculations possible.

Many authors agree that these temperature differences also show the extreme variability of multiscaling. In fact, Krachman et al. claim that they have found an exact solution to the multiscaling problem that is robust under small changes in the way the flow is set up. They calculate the probabilities of outlier events, those with either exceptionally large or exceptionally small temperature differences. Their calculation implies that thermal mixing is, at some points in space and time, much less effective than one might expect on the basis of normal probability distributions.

If true, this would be a notable breakthrough indeed. The authors do point out possible weak points in their argument, but on balance they make a strong, almost compelling case for their result, especially as their numerical simulations back up their main conclusions. Nevertheless, other authors look at the problem slightly differently, and fail to find the claimed results and/or robustness.

There is a real disagreement here. The difficult technical issues will not be settled in a day, but once they are settled we can expect a considerable advance in our understanding and control of mixing processes in swirly fluid flows, aiding the design of all kinds of devices which use turbulence, from aeroplanes to chemical-reaction vessels.

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CIRCADIAN RHYTHMS

Ion channels get the message

Joseph S. Takahashi

Over the past few years, we have learned a great deal about circadian clocks and how they function, both at the organellar and the molecular levels. We know that circadian pacemakers are discretely localized and can be isolated for study in vitro; that these pacemakers are cell autonomous; and that the fundamental molecular elements of the clock mechanism can and are being defined. Analogous mechanisms hold for the frequency gene in the fungus Neurospora. Nonetheless, we still know very little about how the circadian molecular machinery gets its message to the cell membrane and to other cells.

On page 165 of this issue, D'Souza and Dryer report the discovery of a previously undescribed class of cationic channel, called JLO — for 'long open time' — that is under direct circadian control in chick pineal cells. The channel is nonselective for cations, has an intermediate unitary conductance (40 pS) with an unusually long open time, and does not appear to be gated by voltage or soluble second messengers. Most notably, D'Souza and Dryer find that the channel is active at night but not during the day in chick pineal cells maintained on light-dark cycles, and that the rhythm in channel activity persists in constant darkness in vitro. Previous work has suggested circadian regulation of a K+ conductance in molluscan circadian pacemaker cells, but to my knowledge the experiments by D'Souza and Dryer are the first description, at the single-channel level, of an ionic channel that is under direct circadian regulation.

In vertebrates, circadian pacemakers are located in three structures in the central nervous system. These are the hypothalamic suprachiasmatic nucleus, the pineal gland and the retina. In each of these tissues, circadian rhythms can be expressed at the cellular level in vitro, suggesting that in multicellular organisms the circadian clock is a cellular entity and that an ensemble of cellular circadian oscillators act in concert to generate coherent pacemaker output at the tissue level.

Arguably, the chick pineal is one of the best cellular model systems for a vertebrate circadian oscillator, because each cell (pinealocyte) contains all the elements of a circadian system—a photoreceptive entrainment pathway; a circadian oscillator; and an output pathway that regulates a rhythm in the biosynthesis of the now infamous molecule melatonin, a hormone implicated in signalling diurnal and seasonal information in vertebrate organisms. Interestingly, chick pineal cells express a photosensitive pigment called pineal-opsin, as well as a number of retinal photoreceptor-specific proteins including a cyclic-GMP-activated channel.

The rhythm in melatonin synthesis is controlled at the level of an enzyme, arylalkylamine N-acetyltransferase (NAT), which is regulated in part by a circadian rhythm in abundance of messenger RNA. In chick pineal cells, NAT is positively regulated by both cyclic AMP and the intracellular concentration of calcium ions, [Ca2+]i, which act synergistically. There is a circadian rhythm in cAMP levels which is generated endogenously in chick pineal cells, and evidence for an increase in [Ca2+]i, and Ca2+-calmodulin-